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EXAMINER
ARTHUR, LISA BENNETT

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1634	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. ~~09/086,285~~ 09/836,278	Applicant(s) MACK, DAVID H	
	Examiner Lisa B. Arthur	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *08 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-32,34-37, 39-40, 44-129* is/are pending in the application.

4a) Of the above claim(s) *1-10,18-28,39,40 and 44-129* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *11-17,29-32 and 34-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. This action is in response to the election filed March 8, 2002. Currently, claims 1-32,34-37,39,40, 44-129 are pending, but claims 1-10, 18-28, 39, 40 and 44-129 have been withdrawn from prosecution by the restriction requirement made in February 8, 2002 office action. Applicant should note that upon further consideration groups II and IV have been rejoined. Consequently, this action contains an examination of claims 11-17, 29-32 and 34-37.

2. Applicant's election without traverse of Group II, claim 11-17 and 29-32 in Paper No. 10 is acknowledged.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 16, 17 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 16 and 17 are indefinite over the recitation of "expressed higher" and "expressed lower" because "higher" and lower is relational term which requires definition of what the expression is being compared. That is the claims do not make clear to what the higher or lower expression is being compared.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 11, 12, 14-16, 29-30, 32 and 34-35, 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sanchez-Beato et al. (J. PATHOLOGY 1996, 180:58-64) in view of Velculescu et al. (Clinical Chem, 1996 6:858-868.)

Sanchez-Beato et al. Teach a method for detecting a functional mutation in a target up-stream regulatory gene, i.e. p53, comprising preparing a reference sample from reference cells, i.e. peripheral blood lymphocytes (PBLs) having a wild-type upstream regulatory gene (page 58, right column, lines 1-3), preparing a target sample from target cells suspected of having a mutation in said target up-stream regulatory gene , i.e. Hodgkin's disease lymphoid tissue (page 59, right column, third and fourth full paragraphs),detecting the expression f a plurality of down-stream genes, i.e. MDM2 and p21 in said reference and target samples to obtain reference and target expression patterns and comparing said target and reference expression patterns to detected a

functional mutation of said target gene (page 59, right column, third and fourth full paragraphs, page 60, right column, first full paragraph, figure 3). Sanchez-Beato et al. teach the method wherein said downstream genes are transcriptionally regulated by said up-stream regulatory gene (page 58, right column, first paragraph, lines 1-7 and second paragraph, lines 1-4) and wherein expression patterns are detected by measuring transcripts of said down-stream genes (page 59. right column, last 3 paragraphs and page 63, Figure 4, figure legend, line 5) (limitation of claim 12,30, 34). Sanchez-Beato et al. Teach the method wherein the reference and target expression patterns are detected by measuring the amount of protein products and down-stream genes)page 62, Figure 3) (limitation of claim 14). Sanchez-Beato et al. Teach the method further comprising detecting the expression of a plurality of control genes, i.e. GADPH (Figure 4) and actin (Figure 3) and comparing reference and target expression patterns of the control genes to provide a baseline for detecting a significant difference in expression patterns (limitation of claim 15). Sanchez-Beato et al. teach loss of wild-type p53 function precludes overexpression of MDM2 and p21 because high levels of MDM2 and p21 are seen in association with wild-type p53 (page 63, lines 6-9) (limitation of claim 16). Sanchez-Beato et al. Teach a method of detecting a p53 functional mutation in target cells, i.e. Hodgkins disease lymphoid tissue, the method comprising preparing a reference sample from reference cells, i.e. peripheral blood lymphocytes having a wild type p53 gene (page 59), detecting the expression of a plurality of downstream genes, i.e. MDM2 and p21, in said reference and target cells to obtain reference and target expression patterns and comparing said target and

reference expression patterns to detect a functional mutation of p53 (Figure 3). Sanchez-Beato et al. Teach that the down-stream genes comprise p53 upregulated p21 and p53 down-regulated PCNA (page 58) (limitation of claim 32,37). Sanchez-Beato et al. Teach a functional assay for a p53 sequence alternation comprising preparing a target sample from a cell having a p53 sequence alteration , i.e. Saos-2 (page 59. left column, second full para, lines 4-5), preparing a reference sample from reference cells having a wild-type p53, i.e. PBLs (page 59), detecting the expression of a plurality of down-stream genes, i.e. MDM2 and p21 in said reference and target cells to obtain reference and target expression patterns and comparing said target and reference expression patterns to determine the function of said p53 sequence alteration (Figure 3).

Sanchez-Beato et al. does not teach detecting the expression of more than 5 downstream genes and they do not teach detecting all of the p53 regulated genes comprising gadd45, cyclin G, bax, IGF-BP3, thrombospondin, and c-myc, along with p21 and PCNA. However, Velculescu et al. teach that the p53-regulated genes comprising gadd45, cyclin G, bax, IGF-BP3, thrombospondin, and c-myc were known in the art and that their p53 response was routinely studied in the art at the time the claimed invention was made (page 861, left column, Table 2).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to have modified the method of Sanchez-Beato et al. with the teachings of Velculescu et al. in order to have achieved the expected benefit of globally detecting p53-mediated changes in the cell since Velculescu et al. taught that p53 was known to

be the most mutated gene in human cancer (page 859, left column, second full paragraph). The ordinary artisan would have been further motivated to have included all of the known p53 regulated genes in to the method of Sanchez-Beato et al. because the ordinary artisan would have known that the resulting expression profile would have been expected to be significantly more informative with 8 genes than it would have been with only 2 in the profile.

7. Claims, 13, 31 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sanchez-Beato et al. in view of Velculescu et al. as applied to claims 12, 30 and 35 above, respectively, and further in view of Brown et al (5,807,522).

Neither Sanchez-Beato et al. or Velculescu et al. teach the method wherein the transcripts are detected with a high density nucleic acid array. However, detection of transcripts with a high density nucleic acid array was known in the art as taught by Bornw et al. Specifically, Brown et al. teach a method for detecting a mutation omprising preparing a reference sample from reference cells (col. 17, lines 56-59), preparing a target sample from target cells (col. 17, lines 60-61), detecting the expression of a plurality of genes in said reference and target samples to obtain reference and target expression patterns to thereby detect a mutation (col. 18, lines 10-12) and wherein the expression patterns are detected by measuring the amount of transcripts with a high density nucleic acid array (Example 2, col. 15, lines 5-17).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Sanchez-Beato

et al. in view of Velculescu et al. to include the teaching of Brown et al. to obtain the claimed method as a whole because the ordinary artisan would have been motivated with a reasonable expectation for success because Brown et al. taught that with an array at least 10 to the third distinct nucleotide sequences could be detected simultaneously (Brown et al., col. 14, lines 19-20). The ordinary artisan would have immediately seen that the array of Brown et al. Would have provided the expected benefit of analyzing the plurality of p53 regulated genes simultaneously for the obvious benefit of economy of time and labor over electroporation and transfer to nylon membranes of Sanchez-Beato et al.

8. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sanchez-Beato et al. in view of Velculescu et al. as applied to claim 11 above, and further in view of Lewin (Genes V, 1994, page 76).

Neither Sanchez-Beato et al. nor Velculescu et al. teach the method further comprising indicating a gain of function mutation in said target gene if a significant portiopn of said down-regulated genes are expressed relatively lower in the target sample or if a significant portion of up-regulated genes are expressed higher in the target. However, gain of function mutations were known to the ordinary artisan at the time the claimed invention was made wherein a mutation which causes a protein to acquire a new function is termed "a gain of function" mutation as taught by Lewin.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the teaching of Lewin et al. to

interpret the gene expression obtained in the method of Sanchez-Beato et al. in view of Velculescu et al. as a gain of function mutation for the expected benefit of interpreting, understanding and communicating to others in the art complete experimental results.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11-17, 29-32, 34-37 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,303,301 in view of Velculescu et al.

The claims are drawn to a method for a functional mutation is a target upstream regulatory gene, specifically in p53, by making a reference sample having a wild type up-stream regulatory gene, i.e. p53, and a target sample from cells from suspected of having a mutation in this gene, detecting expression of more than 5 down-stream genes in the reference and the target and comparing to detect functional mutations or inactivation of the target gene. The claims of patent 6,303,301 are drawn to the same method except that it is further limited only p53, using downstream genes, gadd45,

cyclin G, p21, Bax, IGF-BP3 thrombospondin and c-myc and wherein loss of function is detected if expression in up-regulated genes is 5 times less in target cells or expression of down-regulated genes is at least 5 times more in target cells. The claims of the instant application broadly encompass the claims of patent 6,303,301 and consequently, the claims of this application and the claims of the patent contain overlapping subject matter.

9. No claims are allowable over the prior art.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa B. Arthur whose telephone number is (703) 308-3988. The examiner can normally be reached on Monday and Tuesday from 7:00 a, to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP 1800